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OPINION

# COVID-19 and Flu Pandemics Follow a Pattern: A Possible Cross-immunity in the Pandemic Origin and Graver Disease in Farther Regions

Alireza Bolourian[a] and Zahra Mojtahedi[b]

[a]College of Pharmacy, Oregon State University, Corvallis, Oregon, USA
[b]Department of Health Care Administration and Policy, School of Public Health, University of Nevada, Las Vegas, Las Vegas, Nevada, USA

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So far, the COVID-19 pandemic has caused less casualty in Eastern Asia areas compared to the other parts of the world. The pattern of less casualty in the pandemic origin has also been observed in the three main flu pandemics in the last century. It is reasonable to speculate that less casualty of COVID-19/flu in the pandemic origin is likely due to the preexisting cross-immunity to some close viruses being more prevalent in those regions. Experts and modelers should scale up the severity of a flu-like viral epidemic to predict its real severity for the rest of the world. © 2021 IMSS. Published by Elsevier Inc.

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It has been eight months since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was originated from China around December 2019. All the countries in East Asia, Southeast Asia, and North Asia have experienced a lower rate of the disease and mortality irrespective of their health care systems. For example, Japan and South Korea, similar to Thailand and Vietnam, have a lower COVID-19 rate/mortality. Even, highly populated countries in that region, such as the Philippines and Indonesia, have lower COVID-19 rates/mortality compared to developed countries such as Germany and Scandinavian countries (1). Intriguingly, the pattern of a graver disease in geographic regions far from the pandemic origin has been observed in the three previous flu pandemics in 1918, 1957, and 1968 (2,3). While the 1918 pandemic, also known as the Spanish flu, was likely originated from the USA, it took more lives in other continents, such as Asia and Europe. The 1957 and 1968 flu pandemics started in China but caused much more mortality in the USA and Europe (2,3).

The increased COVID-19/flu aggressiveness in regions far from the pandemic origin cannot be fully explained by obesity, comorbidities, and age, the certain factors contributed to COVID-19/flu aggressiveness in the same geographic region (4). The highest mortality for COVID-19 is among elderly population (1,5). However, Japan has the oldest population of the world, but it still has a very low rate/mortality of COVID-19 (1). A compelling explanation for the pattern might be a partial preexisting cross-immunity to SARS-CoV-2/influenza viruses in areas close to the origin of the pandemics (6,7). Substantial data exist on preexisting cross-immunity, either cross-reactive antibodies or T-cells, to influenza viruses. For example, preexisting, cross-reactive T-cells have been demonstrated to be protective against a flu disease. As a large-scale example, the less grave 1968 flu pandemic was likely due to the cross-immunity from the 1957 pandemic (3). In the case of COVID-19, much more data is still required to conclude about preexisting cross-immunity in different populations. Reports on T-cell reactivity against SARS-CoV-2 in healthy donors with no cross-antibodies to SARS-CoV-2 are emerging in recent months. In Germany, Braun et al., comprehensively investigated SARS-CoV-2 spike glycoprotein (S)-reactive CD4+ T-cells in peripheral blood of COVID-19 patients as well as healthy donors with no exposure to the virus. They detected S-reactive CD4+ T-cells in 83% of COVID-19 patients and 34% of seronegative healthy donors (6). There are similar very recent reports on T-cell reactivity against SARS-CoV-2 from other countries as well (6). It has been speculated that the SARS-CoV-2-specific T-cells in unexposed individuals

Address reprint requests to: Zahra Mojtahedi, MD, PhD, University of Nevada Las Vegas, School of Public Health, University Gateway Building, 4700 S. Maryland Pkwy. Ste. 335, Las Vegas, NV 89119, USA; Phone: +17028955090; FAX: +17028955184; E-mail: mojtahed@unlv.nevada.edu

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might originate from memory T-cells derived from exposure to ''common cold'' coronaviruses, such as HCoV-OC43 and HCoV-229E (6). Whether the preexisting cross-reactivity to COVID-19 is associated with protection or pathology needs more investigation (6).

So far, no genetic factors explaining the lower COVID-19 rate/mortality in East Asia areas have been identified. It is reasonable to speculate that a lower rate/mortality of COVID-19 in East Asia is likely due to the preexisting cross-immunity (either reactive antibodies or T-cells) to some close viruses being more prevalent in those regions. A large-scale, multi-center analysis of preexisting cross-immunity across the world will clarify this hypothesis. However, we cannot wait years for these data to be completed since another pandemic might be originating somewhere else. Indeed, the failure of the WHO to send warning early in the COVID-19 pandemic might be owing to a lower rate and mortality of COVID-19 in East Asia. Modelers should consider the possibility that flu-like epidemics may cause a graver disease in regions farther to the origin of the disease. Scaling up the disease rate/mortality early in the epidemics might therefore authentically estimate the severity of the disease for the rest of the world.

Preexisting cross-immunity against a virus in many healthy people and a vast area may also indicate that a milder form of the virus has been circulating in the community for quite some time before the emergence of a wilder form. If preexisting cross-immunity (either reactive antibodies or T-cells) is detected at the beginning of an epidemic among local people, it may be interpreted as a graver disease in far areas, where no cross-immunity exists, and the corresponding models should be scaled to forecast the factual rate/mortality of the disease for the rest of world.

In conclusion, the COVID-19 pandemic and the three main flu pandemics in the last centuries follow a similar pattern: the farther from the pandemic origin, the graver the disease. For the future, health experts and modelers should scale up the severity of flu-like epidemics to better predict the disease severity in a pandemic and send early warning based on factual scaling.

## Conflict of Interests

The authors declared no potential conflicts of interest.

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